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Research Article

The relationship between first trimester systemic inflammatory markers and elevated uterine artery pulsatility index

Gebeliğin birinci trimesterinde sistemik inflamatuar belirteçler ile yüksek uterin arter pulsatilite indeksi ilişkisi

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Abstract

Introduction: Preeclampsia is a serious complication of pregnancy leading to maternal and perinatal morbidity and mortality. The etiopathogenesis still remains unsolved, however, various theories currently become well-proved. The leading etiopathogenetic mechanisms are impaired placentation, and placental hypoxia, immune mechanisms, systemic inflammatory reaction, endothelial damage and maternal cardiovascular maladaptation. These mechanisms overlap and induce each other. There are some preventive interventions only if the patients at high-risk are identified timely. This study aimed to investigate the relationship between the inflammatory pathway and placental insufficiency in the first trimester, utilizing the clinical markers of both. It also aims to find out a cheap and easy test to identify those who absolutely need to undergo a comprehensive risk assessment.

Methods: This retrospective observational study included 28 patients with high uterine artery resistance (pulsatility index >90th centile) in the first trimester as study group and 67 patients with normal uterine artery resistance in the first trimester as control group. The two groups were compared in terms of risk factors for preeclampsia. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio as systemic inflammatory markers were compared between the groups. ROC analysis was performed to obtain a cut-off value for predicting high uterine artery pulsatility index.

Results: Demographic data, anamnestic and examination risk factors for preeclampsia did not differ between the groups. However, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were significantly higher in the patients with uterine artery pulsatility index above 90th centile. A cut off value of 3.58 and 136.9 of Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio, respectively were determined for predicting first trimester uterine artery pulsatility index above 90th centile.

Conclusions: Neutrophil/lymphocyte and platelet/lymphocyte ratio can simply be used to identify the patients who need referral for uterine artery doppler assessment.

Keywords: preeclampsia, uterine artery, pulsatil flow, neutrophil, lymphocyte, placenta

Öz

Giriş: Preeklampsi, gebeliğin ciddi bir komplikasyonudur ve maternal ve perinatal morbidite ve mortalitenin önde gelen nedenlerindendir. Etiyopatogenez hala çözülememiştir, ancak çeşitli teoriler artık iyice kanıtlanmıştır. Başlıca etyopatogenetik mekanizmalar defektif plasentasyon, plasental hipoksi, immün mekanizmalar, sistemik inflamatuar reaksiyon, endotel hasarı ve annenin gebeliğe kardiyovasküler maladaptasyonudur. Bu mekanizmalar birbiriyle örtüşür ve birbirini tetikler. Yüksek riskli hastaların zamanında tespit edilmesi durumunda işe yarayabilecek bazı önleyici müdahaleler mevcuttur. Bu çalışma, her ikisinin de klinik belirteçlerini kullanarak, ilk trimesterde inflamatuar yolak ile plasental yetmezlik arasındaki ilişkiyi araştırmayı amaçladı. Ayrıca kapsamlı bir risk değerlendirmesinden geçmesi gereken kişileri tespit etmek için ucuz ve kolay bir test bulmayı da amaçladı.

Yöntem: Bu retrospektif gözlemsel çalışmaya, ilk trimesterde uterin arter direnci yüksek (pulsatilite indeksi >90. persantil) olan 28 hasta çalışma grubu olarak ve ilk trimesterde uterin arter direnci normal olan 67 hasta kontrol grubu olarak dahil edildi. İki grup preeklampsi risk faktörleri açısından karşılaştırıldı. Sistemik inflamatuar belirteçlerden nötrofil/lenfosit oranı ve trombosit/lenfosit oranı gruplar arasında karşılaştırıldı. Yüksek uterin arter pulsatilite indeksini öngörmek için bir kesim değeri elde etmek amacıyla ROC analizi yapıldı.

Bulgular: Preeklampsiye ilişkin demografik veriler, anamnez ve muayeneye dayalı risk faktörleri gruplar arasında farklılık göstermedi. Ancak uterin arter pulsatilite indeksi 90. persantilin üzerinde olan hastalarda nötrofil/lenfosit oranı ve trombosit/lenfosit oranı anlamlı olarak yüksekti. Birinci trimester uterin arter pulsatilite indeksinin 90. persantilin üzerinde olduğunu predikte edebilecek nötrofil/lenfosit oranı ve trombosit/lenfosit oranının sırasıyla 3,58 ve 136,9 kesme değeri olduğu belirlendi.

Sonuç: Nötrofil/lenfosit ve trombosit/lenfosit oranı, uterin arter doppler değerlendirmesi için sevk edilmesi gereken hastaların belirlenmesinde basitçe kullanılabilir.

Anahtar Kelimeler: preeklampsi, uterin arter, pulsatil akım, nötrofil, lenfosit, plasenta

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Key Points

1. Impaired spiral artery remodeling is closely related with systemic inflammation
2. The patients at risk for high uterine artery pulsatility index in the first trimester can be predicted with systemic inflammation markers obtained from simple blood count.

Introduction

Preeclampsia is one of the most common and serious complications of pregnancy. It complicates 2-8% of the pregnancies varying between the countries [1]. Despite recent preventive interventions, it is still one of the most common reason of maternal severe morbidity, mortality, and perinatal complications [2]. The etiopathogenesis of preeclampsia still remains indefinite although it occupies a considerable number of research in maternal-fetal medicine, immunology, genetics and biochemistry. Therefore, preeclampsia is one of the major 'obstetrical syndromes'. There are multiple and overlapping theories leading to a common pathway consisting of systemic inflammation, endothelial damage and inadequate placental perfusion. The role of placental ischemia is well- established since there is a solid body of evidence [3]. Remodeling of the uterine arteries by the invasion of trophoblasts is the key stone of adequate placental perfusion. Impaired invasion of the spiral arteries by the trophoblasts and inadequate remodeling leads to pathological narrowing of the spiral arteries, placental ischemia-reperfusion injury and hypoxia in the uteroplacental unit [4].

It is known that defective placentation results in raised uterine artery impedance [5]. Abnormal uterine artery flow pattern was shown to be related with high ischemic score and placental infarctions [6]. High resistant uterine artery Doppler measures in the first trimester are clearly associated with impaired endovascular trophoblastic invasion and increased risk of adverse pregnancy outcomes secondary to placental dysfunction [7]. Elevated first trimester uterine artery Doppler PI above 90th centile is detected in 77% of the cases of early preeclampsia [8].

Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have been shown to be good markers for subclinical inflammatory diseases [9]. They are also detected to be promising markers for both systemic inflammation and thrombosis [10].

Considering the relationship between defective placentation, hypoxia in the maternal-fetal interface and systemic inflammation, this study investigates the relationship between systemic inflammation markers namely neutrophil/lymphocyte ratio (NLR) and platelet/ lymphocyte ratio (PLR) and uterine artery pulsatility index (PI).

Methods

This study was conducted retrospectively among the patients 95 cases who underwent 11- 14 weeks aneuploidy screening test at a tertiary maternal fetal medicine center between January 2023 and July 2023. All eligible patients who applied for 11- 14 weeks aneuploidy screening test during the study period, underwent total count of blood cells at the same visit and has complete examination records to exclude any suspect of an active infection or any inflammatory diseases at the time of enrollment were included in the study. It was approved by the ethics committee of Health Sciences University, Zeynep Kamil Women and Children Diseases Research Hospital with the decision number 7 (date:11.01.2023). As routine clinic protocol, the patients were screened for preeclampsia risk by anamnesis, blood pressure (BP) assessment and uterine artery Doppler measurement. The patients gave blood sample for aneuploidy screening test and other first trimester routine tests including total count of blood cells (CBC). To measure the pulsatility index (PI) of the uterine artery, 3.5 -5 MHz curvilinear transabdominal transducer was placed suprapubic in a midsagittal plane of the uterus and the cervical canal was visualized. Transducer was slightly moved to the lateral and the color flow Doppler was activated. The uterine arteries were seen as aliasing vessels along the cervix. Pulsed wave Doppler was activated, the sample gate was set to 2 millimeters, flow velocity waveforms from the ascending branch of the uterine artery at the closest point to the internal cervical os were obtained. Care was taken not to have an angle of insonation greater than 30^0. The PI was measured when three similar consecutive waveforms were obtained. Data regarding the anamnesis, mean arterial pressure (MAP), CBC results and uterine artery PI values were obtained from the computerized data base including the records of examination and laboratory results. Mean uterine artery PI was calculated with the formula (systole + (2x diastole))/3. The patients with uterine artery PI>90. percentiles were allocated to study group and those with uterine artery PI<90.percentiles were allocated to control group. The examination records of each patient were reviewed about any complains or examination findings pointing acute or chronic infections which could affect the laboratory results. The patients with chronic diseases were excluded with the same consideration. Systemic inflammatory markers namely neutrophil/lymphocyte ratio (NLR) and platelet to ratio (PLR) were compared between the groups.

Ethical approval

Ethics committee of Health Sciences University, Zeynep Kamil Women and Children Diseases Research Hospital approved the study. Application title: 'Investigating the impact of hemorheological parameters on development of preeclampsia in the patients at high risk'. Decision number 7 (date:11.01.2023).

Informed consent

An informed consent was not taken due to the retrospective observational design of the study.

Permissions: Permission to use the hospital data for this study was taken from Zeynep Kamil Women and Children Diseases Research Hospital obstetrics and gynecology department.

Statistical analysis

The normality of the data was confirmed using the Kolmogorov Smirnov test. The significance of between-group differences was evaluated using the independent-samples t-test for normally distributed data. Mann-Whitney U test was used to compare the non-normally distributed data. The Chi-square test or Fisher's exact test was used to compare the proportions of risk factors for preeclampsia between the groups. Categorical variables were expressed as n (%) and Mann-Whitney U test was used for descriptive analysis. Receiver operating characteristic (ROC) curves were used to determine the potential prognostic value of the NLR and PLR. The area under the ROC curve (AUC) with 95% confidence interval (CI), sensitivity, and specificity are presented. P value below <0.05 was considered significant. Statistical analyses were conducted with SPSS software (ver. 22.0; IBM Corp., Armonk, NY, USA).

Results

A total of 95 cases were included in the study. Median maternal age was 31 (19-42). The study group included 28 cases and control group included 67 cases. There was no significant difference in terms of maternal age, gravidity, parity, abortions, body mass index, chronic diseases namely

chronic hypertension, diabetes, renal insufficiency and autoimmune diseases between the study and control groups. There was also no significant difference in terms of personal or familial history of preeclampsia (Table 1).

Table 1. Comparison of demographic features and risk factors for preeclampsia between the groups

Characteristic	Total (n= 95)	PI < 90th centile (n= 67)	PI ≥ 90th centile (n= 28)	p-value[2]
Age (median (min-max))	31.0 (19-42)	31.0 (22-42)	31.0 (19-42)	0.854
Gravidity (median (min-max))	2 (1-9)	2(1-7)	2 (1-9)	0.644
Parity (median (min-max))	1 (0-6)	1 (0-4)	0 (0-6)	0.131
Number of abortions (median (min-max))	0 (0-6)	0 (0-4)	0 (0-6)	0.181
Chronic hypertension n(%)	5(5.3)	2(3)	3(10.7)	0.190
Diabetes n(%)	5(5.3)	3(4.5)	2(7.1)	0.630
Autoimmune diseases n(%)	1(1.1)	0	1 (0.03)	1.000
Renal insufficiency n(%)	0(0)	1(1.5)	0(0)	1.000
Prior preeclampsia n(%)	8(8.4)	5(7.5)	3(10.7)	0.690
Familial preeclampsia history n(%)	7(7.4)	4(6)	3(10.7)	0.417

Mann-Whitney U test was used to compare the data. The Chi-square test was used to compare the categorical variables between the groups.

Mean arterial pressure was 86.28±11.79 mmHg in the study group and 84.9±8.2 mmHg in the control group. The difference was statistically insignificant. Regarding the blood count parameters, the only significant difference between the study and control groups were observed in neutrophil count and lymphocyte count (Table 2).

Table 2. Comparison of examination findings and laboratory results between the groups

Examination finding/ test results	Total (mean±SD) n=95	PI < 90th centile (mean±SD) n = 67	PI ≥ 90th centile (mean±SD) n = 28	p-value[2]
GA at the time of scan	12.16 ±1.53	12.05±1.7	12.46 ±0.96	0.261
BMI (kg/m^2)	26.77±4.59	27.02±4.6	26.20±4.60	0.298
Systolic pressure (mmHg)	111.96±11.33	111.40±9.60	113.28±14.85	0.287
Diastolic pressure (mmHg)	71.96±9.74	71.60±8.80	72.78±11.85	0.225
MAP	85.32±9.36	84.91±8.21	86.28±11.79	0.138
RBC 4-5,50	4.33±0.33	4.32 ±0.33	4.32 ±0.29	0.480
HGB (g/dl)	12.29±1.03	12.41 ±0.93	12.29±0.77	0.838
HCT (%40-54)	36.92±2.91	37.14 ±2.7	36.90 ±2.32	0.919
MCV (fL 80-100)	85.64±6.93	85.42±8.74	85.72±3.91	0.253
MCH (pg 27-34)	28.60±1.89	28.73±1.86	28.55 ±1.53	0.147
MCHC (g/dl 30-36)	33.27±0.79	33.38± 0.70	33.23 ±0.86	0.426
RDW	13.91±1.27	13.77 ±1.32	13.54±0.54	0.493
PLATELET	257.88±63.56	262.14 ±62.71	257.1±60.9	0.841
WBC 4-10 (10*3/ul)	9.49±2.26	9.44±1.86	9.80 ±1.49	0.248
NEU	6.93 ±1.98	6.64 ±1.79	7.62 ±2.28	0.044
LYMPH	1.98±0.62	2.1±0.61	1.7±0.55	0.004

PI: Uterine artery pulsatility index, GA: gestational age, BMI: body mass index MAP: mean arterial pressure, RBC: red blood cell, HGB: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, WBC: white blood cell, NEU: Neutrophil, LYMPH: lymphocyte.
Mann-Whitney U test was used for non-normally distributed, and independent-samples t-test was used for normally distributed data to compare the data between the groups.

First trimester SIR markers were demonstrated in Table 3. Systemic inflammation markers significantly differed between the groups. NLR and PLR were significantly higher in the patients with high uterine artery PI ($p<0.001$ and $p<0.005$, respectively).

Table 3. Comparison of NLR and LPR between the groups.

Test result	PI < 90th centile (n = 67)	PI ≥ 90th centile (n = 28)	p-value[2]
WBC 4-10 (10*3/ul)	9.44±1.86	9.80 ±1.49	0.248
NLR	3.31±0.97	5.14±3.41	**<0.001**
PLR	128.53±35.25	168.83 ±81.62	**0.005**

PI: Uterine artery pulsatility index, WBC: white blood cell, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/ lymphocyte ratio
Mann-Whitney U test was used for non-normally distributed, and independent-samples t-test was used for normally distributed data to compare the data between the groups.

ROC curves were used to derive cutoff values of NLR and PLR to predict the patients with resistant uterine artery flows. The best predictor for uterine artery PI>90th centile was NLR at an optimal cutoff value of 3.58 (area under the curve, 0.751; 95% confidence interval, 0.631–0.871, p<0,001), with a sensitivity of 75% and a specificity of 61.2% (Figure 1).

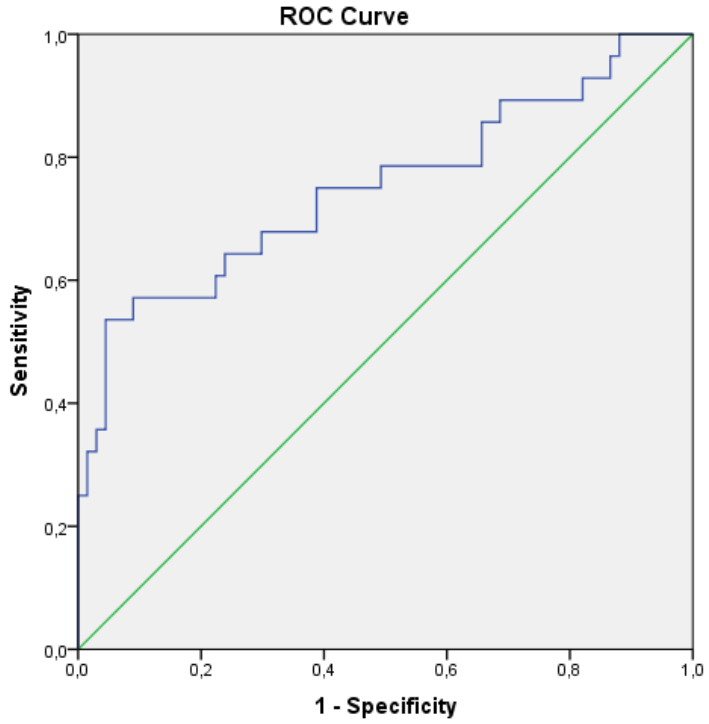

Figure 1. The risk of high uterine artery impedance in at a NLR level of 3.58 (area under the curve, 0.751; 95% confidence interval, 0.631–0.871, p<0,001; sensitivity;75; specificity;61.2). ROC curve, receiver operating characteristic curve

The optimal cutoff value for PLR was 136.9 (area under the curve, 0.684; 95% confidence interval, 0.566–0.803 p<0,001); with a sensitivity of 60.7% and a specificity of 61.2 % (Figure 2).

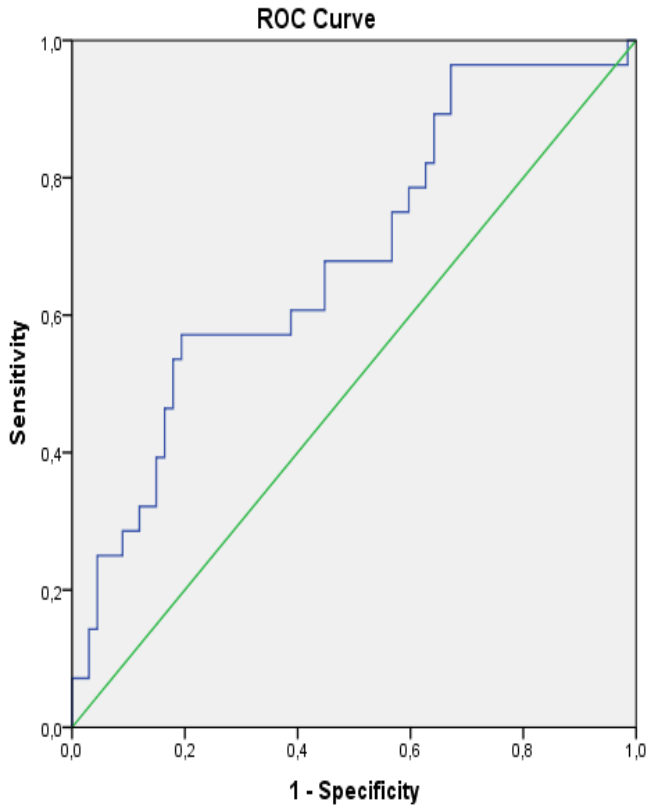

Figure 2. The risk of high uterine artery impedance in at a PLR level of 136.9 (area under the curve,0.684; 95% confidence interval, 0.566–0.803, p:0,005; sensitivity;60.7;specificity;61.2). ROC curve, receiver operating characteristic curve

Discussion

The results of this study support the theories on the relation between systemic inflammation and defective uterine artery remodeling. Adequate implantation of the placenta and trophoblastic invasion of the spiral arteries has a vital role in development of the placenta as an organ which supplies nutrients and oxygen for the fetus. The first stage of placental remodeling occurs between 8-12 gestational weeks in which trophoblasts invade the intradecidual portion of the spiral arteries. The second stage occurs between 14- 18 weeks and includes deeper invasion through the myometrial segments of spiral arteries, the loss of smooth muscle of the spiral arteries which eventually develops a low-resistant and high blood flowed vascular system [4]. Inadequate spiral arteries remodeling and defective placentation results in hypoperfusion of fetoplacental unit. Defective placentation also leads to imbalance of circulating vasoactive factors consecutively leading to maternal vascular maladaptation, systemic endothelial dysfunction and systemic inflammatory response [4,11].

Studies have shown that there is a physiological inflammatory response in the pregnancy as a consequence of immune alterations in the maternal-fetal interface to suppress the immune response of the mother to the fetus [12]. Dysregulation of the endogenous immune response leads to overactivated inflammatory response and vascular endothelial damage which results in hypoxia and subsequently contributes to development of preeclampsia [13]. Hypoxia promotes the production of reactive oxygen species (ROS), triggering the oxidative stress which further enhances the systemic inflammatory response and vascular endothelial damage [14-17]. Another suggested pathway is that; pathological inflammatory changes cause local immune imbalance prohibiting the effective trophoblastic invasion of the spiral arteries which results in placental dysfunction [18]. By any means, systemic inflammation and defective uterine artery remodeling induce each other in the cascade leading to preeclampsia. It is well-reported in the literature that various inflammatory cytokines are significantly elevated in preeclampsia and uteroplacental insufficiency, however, their utility is limited in the clinic due to high costs [16].

Systemic inflammation markers obtained from CBC are recently intensely investigated for numerous chronic diseases from cancers to cardio vascular thrombotic events, autoimmune diseases to chronic inflammatory diseases or sepsis [9]. The reason for this attention to systemic inflammatory response (SIR) markers is that they are cheap and easily measurable. This study showed that first trimester pregnant women with high uterine artery PI have elevated SIR markers namely NLR ratio and PLR. Elevated SIR markers have been shown in the case of preeclampsia in the previous studies [19-20]. NLR is the one particularly focused on, as it is shown to be more elevated in thrombotic events (which also occurs in the maternal-placental interface secondary to inflammation and endothelial damage) and is related to the disease severity in preeclampsia [10, 21]. NLR seems a more valuable marker with a higher sensitivity and a higher AUC value in the cut-off value of 3.58. The reason for insignificance of anamnestic risk factors between the high uterine artery PI group and low uterine artery PI group was most probably the small sample size of the study. The blood pressure measures in the first trimester also did not differ. This was related with the pregnancy physiology which provides a decrease in systolic and particularly diastolic BP secondary to decrease of systemic vascular resistance. This effect would have been less prominent in chronic hypertension patients, however there was no difference regarding chronic hypertension rates between the study and control groups. The relatively small sample size resulted in no significant difference in terms of demographic data including the criteria regarded as high-risk factors for preeclampsia according to the guidelines [22]. Despite this fact, the SIR markers did good in identifying who might possibly have high uterine artery PI and defective placentation.

At present, no targeted therapy exists to blockage or treat abovementioned complex etiopathogenesis of preeclampsia. The only effective preventive method is starting Aspirin before 16th gestational weeks (before the completion of spiral arteries' remodeling and placentation) to diminish endothelial damage, thrombosis and hypoxia in the maternal placental interface [23]. Therefore, identifying the patients at high risk for early-onset preeclampsia is crucial.

Limitations

Retrospective design of the study is the main limitation of the study. In addition, the perinatal outcomes of the study population is not available due to the cross-sectional design.

Conclusion

In the first step obstetric health care, it is important to identify the high- risk patients for timely referral. Universal screening for preeclampsia does not seem to be applicable yet, as all patients don't have the chance to reach tertiary centers. CBC is a routine test run by first step health care providers in the first trimester. In addition to personal and family history and physical examination including blood pressure measurement, it can be beneficial to evaluate NLR and PLR as systemic inflammatory markers to selectively and timely refer the pregnant women for uterine artery Doppler assessment and preeclampsia risk scoring.

Recommendations for future research: Prospective studies to observe the alterations of NLR and PLR in the cases with high uterine artery PI along the pregnancy and to report the outcomes of these pregnancies are needed.

Conflict of interest: The author declares no conflict of interests.

Author Contributions		Author Initials
SCD	Study Conception and Design	LU
AD	Acquisition of Data	LU
AID	Analysis and Interpretation of Data	LU
DM	Drafting of Manuscript	LU
CR	Critical Revision	LU

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